PATENT COOPERATION TREATY

From the:
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	4 FEB 2005
Applicant's or agent's file reference: 502950	FOR FURTHER ACTION: See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/AU2004/001762	16 December 2004	16 December 2003

International Patent Classification (IPC) or both national classification and IPC
Int. Cl. [7] C07K 14/715, C12N 15/12

Applicant
COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION et al

1. This opinion contains indications relating to the following items:

- [X] Box No. I — Basis of the opinion
- [ ] Box No. II — Priority
- [X] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [X] Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos: 69-88

because:

☐ the said international application, or the said claim Nos.

relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos.

are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos.

are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 69-88

An essential technical feature of the invention appears to be the two FnIII-like domains with mutations in them. The claims, however, are not limited to this essential feature of the invention, they simply define any cytokine domain irrespective of whether there are two FnIII-like domains.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	3, 8-10, 13-15, 17, 18, 21-23, 26-28, 34, 39-41, 44-49, 52-54, 57-59, 68, 72-74 and 76-88	YES
	Claims	1, 2, 4-7, 11, 12, 16, 19, 20, 24, 25, 29-33, 35-38, 42, 43, 50, 51, 55, 56, 60-67, 69-71 and 75	NO
Inventive step (IS)	Claims	3, 13-15, 17, 18, 21-23, 27, 28, 44-49, 54, 58, 59 and 68	YES
	Claims	1, 2, 4-12, 16, 19, 20, 24-26, 29-43, 50-53, 55-57, 60-67 and 69-88	NO
Industrial applicability (IA)	Claims	1-88	YES
	Claims	None	NO

2. Citations and explanations:

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1: WO 2002/032925 A2 (PHYLOS, INC.)

D2: Chuntharapai. A., et al: The Journal of Immunology (1999); Vol 163: 766-773.

D3: Gustin. S. E., et al; European Journal of Biochemistry (2001); Vol 268: 2905-2911.

D4: Chill. J. H., et al; Structure (July 2003), Vol 11: 791-802.

NOVELTY:
The invention lies in a binding moiety and methods of producing the binding moiety. The binding moiety comprises of an extracellular cytokine binding domain (CBD) consisting of two fibronectin-like domains that have been modified such that at least one property of the CBD is altered. A number of citations disclose similar CBDs that have altered fibronectin-like domains with altered properties.

D1: Teaches of binding proteins that are derived from fibronectin type III like domains. The proteins are non antibody proteins that have immunoglobulin-like folds including fibronectin type III like domains with randomised loops such that they are capable of binding different compounds. The proteins are derived from naturally occurring mammalian proteins such as cytokine receptors, GCSF receptors etc (Page 4 line 24; page 9, line 7; page 25, line 1) that have mutations. The proteins contain mutations in the loop of the fibronectin domains (Page 20, lines 15-21) that are involved in binding compounds. As such, the citation includes cytokine receptors that would inherently have the structure consisting of a cytokine binding domain and two fibronectin-like domains. The citation also teaches of these proteins having altered properties as compared to the properties of the non mutated proteins. As such the citation discloses all the essential features of claims 1, 2, 4-7, 16, 19, 20, 24, 25, 29-33, 35-38, 50, 51, 55, 56, 60-67, 69-71 and 75.

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Supplemental Box v

In case the space in any of the preceding boxes is not sufficient.

Continuation of 2 (Novelty):

D2: The citation discloses the structure and functional properties of the human IFN-α receptor hIFNAR2 extracellular domain. The hIFNAR2 receptor has a structure typical of a CHR (cytokine homology receptor) module consisting of two fibronectin domains. Although the citation does not specifically disclose the various regions of the receptor as being fibronectin domains, it would be obvious to the PSA that the structure of the receptor would inherently contain the CHR module consisting of two fibronectin domains. A number of mutations were introduced in the receptor at various positions as shown in Tables IV and V. Some of these mutations are found in the loop regions of the fibronectin (FnIII) domains, example K49A, E51A, D52A, R74A, H77A and E78A (Table V), there are also a couple of mutations in the hinge region W101A and I104A (Table V). The mutations showed altered binding properties to antibodies of hIFNAR2 and to hIFN-α 2/1. As such claims 1, 2, 4-6, 11, 12, 19, 20, 31-33, 35-37, 42, 43, 50, 51 and 64-66 are anticipated by this citation.

D3: The citation teaches of the receptor -β_c that is shared by a number of cytokine receptors for example GM-CSF, IL-3 and IL-5. The β_c receptor belongs to the class I cytokine receptor family consisting of two cytokine homology receptor (CHR) modules. Each CHR module consists of two fibronectin domains. The citation teaches of methods of cloning this receptor into a baculovirus system. The citation also teaches of expression and purification of a number of mutations in the receptor (Table 1) that have altered expression patterns (Page 2909, col 1). As such the citation discloses all the essential features of claims 1, 2, 4, 31-33, 35, 62 and 64-66.

D4: The citation is directed to the NMR structure of a class II helical cytokine receptor- IFNAR2. The structure of this cytokine receptor consists of two fibronectin modules connected by a linker. The citation also discloses mutations in two loop regions of the fibronectin module – CC and EF as well as the hinge region. The citation uses NMR studies to look at mutations in these regions that alter the binding affinity of the receptor to IFNα2 (page 797). The studies confirm previous mutagenesis results that show mutations in the loop and hinge regions alter the binding of ligand - IFNα2. As such the citation clearly discloses mutations in the fibronectin region of a cytokine receptor that alters its binding properties, therefore claims 31-33, 36, 37, 42, 43, 50 and 51 are not novel in light of this citation.

INVENTIVE STEP:

Claims 1, 2, 5, 6, 8-12, 19, 20, 26, 39-41, 52, 57, 72-74 and 76-88 are not inventive in light of D1 and D4. The problem addressed by the applicant in the claims is a method of producing a binding moiety that comprises of an extracellular cytokine binding domain (CBD) consisting of two fibronectin-like domains that have been modified such that at least one property of the CBD is altered, the claims also include the binding moiety. Citation D1 and D4 are directed to a similar problem and in searching the art a diligent searcher investigating this problem could reasonably be expected to have found the documents. The citations teaches of cytokine binding domains that have fibronectin-like domains that have been altered such that at least one property of the CBD is altered. The alterations include mutations in the loop regions of the FnIII-like domains.

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Supplemental Box V

In case the space in any of the preceding boxes is not sufficient.

Continuation of 2 (Inventive step):

D1 teaches of mutations in the loop region of the fibronectin region, although it does not specifically disclose the number of residues increased or decreased in the loop region, it clearly discloses the advantage of mutating the loop region. Furthermore, the citation clearly demonstrates the success of preparing sequences that contain the scaffold of Fn domains that has a second sequence containing a loop sequence inserted into it (pages 28-32) to prepare binding moieties that can bind a range of compounds. Although the citation does not specifically disclose the use of CBDs containing fibronectin domains, the PSA would readily appreciate that this technique was particularly well suited to alter CBDs that do have two FnIII-like domains. Therefore the invention claimed in claims 8-10, 20, 26, 39-41, 52, 57, 72-74 and 76-88 appears to disclose nothing more than routine application of standard steps and techniques.

D4 teaches of similar mutations in the loop region of a class II helical cytokine receptor- IFNAR2. Although the citation does not disclose a method for producing these mutations, it provides a sign post to the PSA to modify the FnIII region of a CBD to produce a binding moiety with altered properties. Such application would be a matter of routine well within the skill level of the PSA and comprise an application of routine steps and techniques. Therefore claims 1, 2, 5, 6, 11, 12, 19 and 20 lacks an inventive step.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 69-88 are not fully supported by the specification. The invention lies in a binding moiety that consists of a modified cytokine binding domain that has a first and a second FnIII-like domain. As such, an essential technical feature of the invention appears to be the two FnIII-like domains with mutations in them. The claims, however, are not limited to this feature of the invention, they simply define any cytokine domain irrespective of whether there are two FnIII-like domains. As the prior art includes CBDs with more than two FnIII-like domains, the specification does not provide support to encompass all these CBDs as appropriate to the working of the invention.